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Left Ventricular Systolic and Diastolic Function Assessed With Two-Dimensional and Doppler Echocardiography in "White Coat" Hypertension

JOHANNES SOMA, MD, TOR ERIK WIDERØE, MD, PHD, KETIL DAHL, MD, OLE ROSSVOLL, MD, TERJE SKJÆRPE, MD, PHD

Trondheim, Norway

Objectives. **The aim of this study was to investigate left ventricular function in subjects with "white coat" hypertension, defined as office arterial diastolic pressure ≥90 and ambulatory daytime pressures <140/90 mm Hg.**

Background. **The white coat arterial pressure response may, by influencing left ventricular function, have a confounding effect in studies of heart disease.**

Methods. **Two-dimensional and Doppler echocardiography, combined with the calibrated subclavian arterial pulse tracing, were used to assess variables of left ventricular function in 26 subjects with white coat hypertension, as well as 22 subjects with previously untreated ambulatory hypertension (office arterial diastolic pressure ≥90 and <115 mm Hg and ambulatory daytime diastolic pressure ≥90 mm Hg) and 32 normotensive subjects.**

Results. **In subjects with white coat hypertension, systolic arterial pressure during the echocardiographic examination was significantly higher than ambulatory daytime systolic pressure. This pressure response was positively related to the ratio of the systolic to diastolic pulmonary venous flow peak velocities and to the peak velocity of flow reversion during atrial systole; it was inversely related to the ratio of early to late mitral flow peak velocities. Left ventricular stroke volume, ejection fraction and velocity of circumferential fiber shortening did not differ in the study groups, but left ventricular external work and end-systolic wall stress were increased in the white coat group.**

Conclusions. **The arterial pressure response in subjects with white coat hypertension is associated with increased left ventricular external work, increased end-systolic wall stress and alterations of left ventricular filling but normal ejection fraction and velocity of circumferential fiber shortening.**

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Subjects who have an exaggerated arterial pressure response in the physician's office but normal average 24-h arterial pressures are considered to have "white coat" hypertension (1). The prognosis in this condition, determined by assessment of end-organ damage, appears to be benign (2–4). However, even though the degree of end-organ damage is low, there are features that may indicate a need for careful medical surveillance of such subjects (5). Moreover, such subjects, who may represent 20% to 60% of a hypertensive population (1,5), may be considered as confounders in studies of heart disease as well as in clinical practice.

Information about left ventricular dysfunction is important because it may be a sensitive indicator of hypertensive heart disease (6–8). There are few reports (2,9) on left ventricular diastolic and systolic function in subjects with white coat hypertension.

From the Department of Medicine, Sections of Cardiology and Nephrology, University Hospital of Trondheim, Norway. This work was supported by grants from the University of Trondheim, Trondheim and the Norwegian Council on Cardiovascular Diseases, Oslo, Norway.

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Address for correspondence: Dr. Johannes Soma, Department of Medicine, Section of Cardiology, University Hospital of Trondheim, N-7006 Trondheim, Norway.

The purpose of this study was to investigate left ventricular systolic and diastolic function assessed with two-dimensional and Doppler echocardiography in subjects with evidence of white coat hypertension and to compare the findings with those in subjects with untreated ambulatory hypertension and normotensive subjects. We recruited for this study subjects who, although evaluated as having hypertension by the general practitioner (physician arterial pressures), had "normal" ambulatory daytime arterial pressures (10). However, arterial blood pressures in these subjects were also measured by a nurse according to a standardized procedure on admission to the ward for hypertension in our hospital (clinic arterial pressures) and during the echocardiographic examination (oscillometric arterial pressures).

Methods

Study subjects. The study comprised three groups that did not differ significantly in age, gender and body surface area (Table 1). The *white coat hypertensive group* consisted of 26 previously untreated subjects with diastolic pressure in the general practitioner's office (office arterial pressure) ≥90 mm Hg and ambulatory daytime pressure <140/90 mm Hg (Table 1). The main reasons for referral to the special ward for hypertension in

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Table 1. Group Characteristics

	Normotensive Group (n = 32)	Hypertensive Groups		p Value
		White Coat (n = 26)	Ambulatory (n = 22)	
Men/women	19/13	14/12	13/9	0.9
Age (yr)	48 ± 7	46 ± 13	48 ± 7	0.8
Body surface area (m^2)	1.90 ± 0.20	1.90 ± 0.18	1.95 ± 0.17	0.6
Pressures (mm Hg)				
Office SP		159 ± 19	159 ± 17	0.9
Office DP		98 ± 5	105 ± 5	0.0001
Clinic SP	118 ± 13	143 ± 19*	141 ± 12*	0.0001
Clinic DP	77 ± 6	89 ± 8*	96 ± 6*†	0.0001
Amb 24-h SP		122 ± 7	142 ± 13	0.0001
Amb 24-h DP		79 ± 6	97 ± 7	0.0001
Amb daytime SP		127 ± 7	145 ± 14	0.0001
Amb daytime DP		83 ± 5	99 ± 8	0.0001

*$p < 0.05$ versus normotensive group. †$p < 0.05$ versus white coat hypertensive group. Data presented are mean value ± SD. Amb = ambulatory; DP = diastolic arterial pressure; SP = systolic arterial pressure.

our hospital were a tendency to blood pressure variability, increased heart rate associated with measurement of arterial pressure, young age or because the patient or his physician wanted a more thorough evaluation before initiation of medical therapy. Subjects who fulfilled the inclusion criteria were consecutively referred for echocardiographic evaluation for inclusion in the study. Five of the referred subjects were excluded: one with valvular heart disease, two with a poor echocardiographic window and two who had used antihypertensive medication.

The group with ambulatory hypertension (*ambulatory hypertensive group*) consisted of 22 previously untreated subjects with office diastolic pressure ≥90 and <115 mm Hg and ambulatory daytime diastolic pressure ≥90 mm Hg. These subjects were recruited from general practitioners, who had referred 24 subjects with previously untreated ambulatory hypertension for echocardiography; 2 were excluded because of inappropriate echocardiographic window.

The normotensive group consisted of 32 subjects with diastolic pressure <90 mm Hg measured by a nurse in the clinic. This pressure was determined in accordance with the requirements for the clinic arterial pressure as described later, but was performed on 1 day only. The subjects were randomly selected from healthy employees in the hospital and matched for age and gender with the hypertensive control group.

Exclusion criteria for all groups were evidence of coronary heart disease, heart failure, valvular heart disease, atrial fibrillation, chronic obstructive pulmonary disease, secondary hypertension, other major diseases or use of drugs and inappropriate echocardiographic window.

All subjects gave written informed consent for the investigation, which was approved by the regional ethical committee.

Arterial blood pressure measurements. *Office arterial pressures* were measurements of brachial artery pressures obtained by the physician in the general practitioner's office. The requirements for recording and analysis of these pressures were in accordance with the guidelines from The Norwegian College of General Practitioners (11). If several pressures were presented on admission to the clinic, an average of these was calculated.

Clinic arterial pressures were measured in the clinic by an experienced nurse using a mercury sphygmomanometer. Korotkoff phase V was used to determine clinic diastolic pressures. These measurements, obtained with the subject seated after >15 min of rest, were performed on 3 days, 1 week apart. The two lowest of three readings on each day were averaged and the average of the two lowest averages determined the clinic arterial pressures. Clinic arterial pressures were initially measured in both arms to exclude significant deviations of arterial pressures between the right and left arms. Later the right arm alone was used.

An ambulatory 24-h pressure recording (Oxford Medilog ABP, Oxford Medical) or Suntech Accutracker II, Suntec Medical Instruments) was performed on a normal workday. *Ambulatory 24-h pressures* were defined as the mean of half-hourly recordings from 7 AM to 11 PM and hourly recordings from 12 PM to 6 AM. *Ambulatory daytime pressures* were defined as the mean of half-hourly recordings from 7 AM to 11 PM. Whereas all clinic arterial pressures were measured in the right arm, ambulatory arterial pressures were measured in the left arm except for a few cases in which the right arm was used.

Oscillometric arterial pressures. Right brachial artery systolic and diastolic pressures were recorded with the oscillometric technique (Dinamap 1846 SXP, Criticon) every minute during the Doppler ultrasound study. The two measurements obtained immediately before the Doppler recordings were averaged and used for subsequent analysis.

Echocardiography. All echocardiographic recordings and analyses were performed by the same investigator. An ultrasound scanner (Vingmed CFM 750, Vingmed Sound, Horten, Norway) with a duplex probe (3.25-MHz imaging/2.5-MHz Doppler) was used. The study subjects rested >10 min before they were examined in a left lateral decubitus position. Recordings were performed in end-expiration. A specially designed computer software (Echodisp 4.0, Vingmed Sound) was used for analysis. Doppler, two-dimensional and M-mode echocardiograms were analyzed independently from each other and without knowledge of the arterial pressures, but the category of the subjects was known. Whereas two-dimensional and Doppler echocardiographic recordings of aortic flow were analyzed in all 80 subjects, M-mode echocardiographic recordings were suitable for analysis in 73 subjects and Doppler recordings of mitral and pulmonary venous flow in 75 and 72 subjects, respectively.

Aortic root pressure and flow. The aortic annulus flow velocities were recorded by pulsed Doppler technique from the apical position with the sample volume positioned in the center of the outflow tract just at the annulus, obtaining an optimal flow velocity spectral profile and a distinct valve closure signal. Data from at least three consecutive cardiac cycles were transferred, together with pulse and electrocardiographic (ECG) tracings, to the computer for analysis. The maximal velocity (i.e., outer envelope of the Doppler spectrum) of at

least three aortic root Doppler flow-velocity curves were traced manually and averaged. The subclavian artery pulse tracings were obtained with a capillary damped funnel (Siemens-Elema AB, Solna, Sweden) positioned over the right subclavian artery at its point of maximal impulse and connected to a strain gauge transducer (model 120-0123, Irex Medical Systems) and displayed simultaneously with the Doppler velocity spectra of the aortic root flow on the monitor (12,13). Only pulse tracings with a consistent wave morphology, a sharp deflection in early systole and a minimal linear drift were used. The pulse tracing was calibrated with oscillometrically obtained systolic and diastolic pressures and the pulse transmission delay corrected by alignment of the pulse tracing incisura to the end-systole of the Doppler flow tracing. The calibrated subclavian pulse tracing closely matches the aortic root pressure (12–14).

Two-dimensional echocardiography. The aortic annulus diameter was measured in the parasternal long-axis view between the insertion points of the valve leaflets by use of the trailing to leading edge method. The left ventricular apical four-chamber, two-chamber, long-axis views and the parasternal short-axis view located at the tip of the papillary muscles were transferred to a computer (Macintosh II series, Apple Computers) as scanline data, that is without loss of ultrasound information, providing a frame rate of 47 frames/s with the standard angle and depth. This provides an excellent condition for reviewing cineloops at different speeds. The endocardial surface in the apical four-chamber view and the endocardial and epicardial surfaces in the short-axis view were traced manually on end-diastolic (the frame according to the R wave on the ECG) and on end-systolic (the frame before opening of the mitral valve) frames according to the convention of Wyatt et al. (15) and Vuille and Weyman (16). The papillary muscles were considered part of the left ventricular cavity. The following variables were determined: the left ventricular long axis (L) measured on end-diastolic (Led) and end-systolic apical four-chamber frames as the distance from the mitral annulus to the apex, the apical part of the end-systolic long-axis (a), truncated at the level of the tips of the papillary muscles, the short-axis end-diastolic (Ded) and end-systolic (Des) diameters, the short-axis end-diastolic (hed) and end-systolic (hes) wall thicknesses and the short-axis end-diastolic (A1ed) and end-systolic epicardial and end-diastolic (A2ed) and end-systolic endocardial areas.

M-mode echocardiography. M-mode echocardiograms of the left ventricle were obtained from the parasternal window, guided by two-dimensional echocardiography. Tracings from the level of the tip of the papillary muscles were transferred to the computer. It was required that the right and left endocardium of the septum and the endocardial and epicardial surfaces of the posterior left ventricular wall be recorded continuously in at least three cardiac cycles. The end-diastolic left ventricular internal diameter (LVIDd), the end-diastolic intraventricular septal thickness (IVSd) and the end-diastolic posterior wall thicknesses (PWTd) were determined according to the Penn convention (17).

Doppler echocardiography of mitral flow and pulmonary flow. Mitral and pulmonary flow velocities were recorded by pulsed Doppler technique, from the apical position, between the mitral leaflets and in the upper right pulmonary vein, respectively. Data from at least five consecutive cardiac cycles were transferred to the computer. The maximal velocity of at least three mitral and pulmonary venous Doppler flow velocity profiles was traced and averaged. From the mitral flow velocity tracings, early mitral flow peak velocity and deceleration time and peak velocity and duration of the late flow were measured. The peak velocity and time-velocity integral during systolic and diastolic pulmonary venous flow and the maximal velocity, velocity integral and duration of the flow reversion during atrial systole were measured.

Analysis of data. Mean aortic pressure (MAP [mm Hg]) was determined as the pressure integral under the calibrated subclavian pressure tracing (12,13). Aortic end-systolic pressure (Pes [mm Hg]) was determined at the incisura of the calibrated pulse tracing. Instantaneous aortic flow ($Q(t)[ml \cdot s^{-1}]$) was calculated as the product of the instantaneous Doppler aortic blood flow velocity and aortic annular cross-sectional area (18). Mean aortic flow ($Q[ml \cdot s^{-1}]$) was calculated as the integral of the instantaneous aortic flow. Left ventricular total power ($W_{tot}[mW]$) was calculated from instantaneous pressure [P(t)] and flow [Q(t)] (19) as follows:

$$\dot{W}_{tot} = \frac{1}{T}\int_0^T P(t)Q(t)\,dt, \quad [1]$$

where T is the duration of the cardiac cycle. Steady power ($\dot{W}_{std}$ [mW]) was calculated from mean aortic pressure and flow:

$$\dot{W}_{std} = MAP \times Q. \quad [2]$$

Oscillatory power ($\dot{W}_{osc}$ [mW]) was calculated as

$$\dot{W}_{osc} = \dot{W}_{tot} - \dot{W}_{std}. \quad [3]$$

Left ventricular end-diastolic (Ved) and end-systolic volumes (Ves) were calculated from two-dimensional echocardiograms according to the following general formula (15,20):

$$V = \tfrac{5}{6} \times A_2 \times L, \quad [4]$$

where V is left ventricular volume, A_2 is the endocardial short-axis area, and L is the long-axis dimension in end-diastole and in end-systole, respectively.

Left ventricular mass was calculated according to an extended version of equation 4 (21–23):

$$LVM_{2D} = 1.05 \times \left\{\tfrac{5}{6} \times A_1ed \times (Led + hed) - \tfrac{5}{6} \times A_2ed \times Led\right\}, \quad [5]$$

where LVM_{2D} = left ventricular mass by two-dimensional echocardiography, 1.05 is the density of the myocardium, A_1ed is the left ventricular epicardial short-axis area, Led is the long-axis dimension, hed is the mean wall thickness, and A_2ed is the endocardial short-axis area, all in end-diastole. Relative wall thickness (RWT [%]) was calculated as 200 × hed/(Ded), where Ded is end-diastolic short-axis diameter. Sphericity index (%) was calculated as 100 × Ded/Led (24). Left ventricular mass was also

calculated from M-mode echocardiograms according to the following formula (25):

$$LVM_{M\text{-}mode} = 1.04\{(LVIDd + IVSd + PWTd)^3 - LVIDd^3\} - 13.6, \quad [6]$$

where $LVM_{M\text{-}mode}$ = left ventricular mass by M-mode echocardiography.

Heart rate was determined from ECG recordings during the echocardiographic investigation. Left ventricular ejection time (LVET [ms]) was determined from the beginning of blood flow to the valve closure click on the aortic Doppler velocity trace and rate corrected (LVETc [ms]) by dividing with the square root of cardiac cycle length. Left ventricular stroke volume (SV) was calculated as Ved − Ves, where Ved and Ves = left ventricular volumes in end-diastole and end-systole, respectively. Left ventricular ejection fraction (EF [%]) was calculated as 100 × SV/Ved. Left ventricular fractional shortening (FS [%]) was calculated as 100 × (Ded − Des)/Ded, where Des = the short-axis end-systolic diameter. Left ventricular velocity of circumferential fiber shortening was calculated as 10 × FS/LVET. Rate-corrected velocity of circumferential fiber shortening was calculated as 10 × FS/LVETc (26,27). Left ventricular meridional (σ_m [kdyn·cm^{-2}]) and circumferential (σ_c [kdyn·cm^{-2}]) end-systolic wall stresses were calculated, respectively, as (28,29):

$$\sigma_m = 1.33\,Pes\left[\frac{Des}{4\,hes\left(1 + \frac{hes}{Des}\right)}\right], \quad [7]$$

$$\sigma_c = 1.33\,Pes\frac{Des}{4\,hes} \times \frac{8a^2 - Des^2}{4a^2 + hes\,Des}. \quad [8]$$

Indexed variables were obtained by dividing with the respective body surface area calculated according to the method of Du Bois and Du Bois (30).

Statistical analysis. Statistical analysis was carried out by using StatView 4.1 software (Abacus Concepts). Continuous variables are expressed as mean value ± SD. Comparisons between groups were performed with one-way analysis of variance. Frequencies were analyzed by Kruskal-Wallis test. When the overall comparison of groups in the analysis of variance indicated significant differences ($p < 0.05$), post hoc comparisons were performed with the Scheffé test. Relations between variables were tested with Pearsons coefficient of correlation. The coefficient of variation (%) was calculated as the standard deviation of the differences divided by the mean of the initial values. The 95% limits of agreement were calculated as the mean difference ± the standard deviation of the differences × 2 (31).

Reproducibility. Intraobserver reproducibility was assessed by comparing measurements in 16 normotensive adults on two occasions, 2 weeks apart. Interexaminer and interanalyzer reproducibility of the noninvasive method have been reported previously (12).

Table 2. Left Ventricular External Work

	Normotensive Group (n = 32)	Hypertensive Groups		p Value
		White Coat (n = 26)	Ambulatory (n = 22)	
Pressures (mm Hg)				
Oscillometric SP	108 ± 12	137 ± 19*	140 ± 11*	0.0001
Oscillometric DP	61 ± 7	75 ± 11*	82 ± 9*†	0.0001
MAP	82 ± 8	103 ± 14*	108 ± 9*	0.0001
Pes	92 ± 10	117 ± 17*	122 ± 10*	0.0001
LVOT (cm)	2.34 ± 0.19	2.30 ± 0.21	2.34 ± 0.16	0.8
Aortic VTI (cm)	23 ± 4	24 ± 4	24 ± 4	0.4
Power (mW)				
Total	1,360 ± 436	1,858 ± 580*	1,974 ± 377*	0.0001
Steady	1,147 ± 351	1,570 ± 498*	1,677 ± 319*	0.0001
Oscillatory	213 ± 107	288 ± 100*	296 ± 81*	0.004

*$p < 0.05$ versus normotensive group. †$p < 0.05$ versus white coat hypertensive group. Data presented are mean value ± SD. LVOT = aortic annulus diameter; MAP = mean aortic pressure; VTI = Doppler velocity-time integral; other abbreviations as in Table 1.

Results

In the white coat group the clinic systolic and diastolic pressures and the oscillometric systolic pressure were significantly higher than the respective ambulatory daytime pressures. These findings indicate that these subjects had a pressure response during measurements of arterial pressures by a nurse and during the echocardiographic examination (Tables 1 and 2). Additional support for a pressure response during echocardiography was provided by the increased left ventricular external work in this group (Table 2).

Left ventricular systolic function evaluated by stroke volume, ejection fraction and fractional shortening did not differ signifi-

Table 3. Left Ventricular Systolic Function

	Normotensive Group (n = 32)	Hypertensive Groups		p Value
		White Coat (n = 26)	Ambulatory (n = 22)	
EDVI (ml·m^{-2})	85 ± 17	83 ± 15	91 ± 16	0.2
ESVI (ml·m^{-2})	35 ± 8	32 ± 9	33 ± 9	0.4
Stroke index (ml·m^{-2})	50 ± 13	51 ± 13	58 ± 14	0.07
Ejection fraction (%)	59 ± 7	61 ± 9	64 ± 9	0.08
Fractional shortening (%)	27 ± 6	28 ± 7	31 ± 11	0.08
Heart rate (beats/min)	64 ± 8	69 ± 12	68 ± 6	0.1
LVET (ms)	310 ± 20	308 ± 24	296 ± 21	0.06
LVETc (ms)	320 ± 20	327 ± 23	315 ± 17	0.16
Vcf (circs^{-1})	0.87 ± 0.19	0.93 ± 0.21	1.06 ± 0.27*	0.01
Vcfc (circs^{-1})	0.85 ± 0.18	0.88 ± 0.19	0.99 ± 0.24*	0.04
σm es (kdyn·cm^{-2})	65 ± 10	78 ± 23*	69 ± 20	0.02
σc es (kdyn·cm^{-2})	155 ± 21	185 ± 47*	168 ± 36	0.009

*$p < 0.05$ versus normotensive group. †$p < 0.05$ versus white coat hypertensive group. Data presented are mean value ± SD. EDVI and ESVI = end-diastolic and end-systolic volume index, respectively; LVET and LVETc = ejection time with and without rate correction, respectively; Vcf and Vcfc = velocity of circumferential fiber shortening with and without rate correction, respectively; σc es = circumferential wall stress; σm es = meridional wall stress.

Table 4. Left Ventricular Dimensions

	Normotensive Group (n = 32)	Hypertensive Groups		p Value
		White Coat (n = 26)	Ambulatory (n = 22)	
MI, 2DE ($g \cdot m^{-2}$)	102 ± 20	106 ± 21	126 ± 22*†	0.0003
DedI ($cm \cdot m^{-2}$)	2.75 ± 0.35	2.73 ± 0.33	2.78 ± 0.30	0.9
hedI ($cm \cdot m^{-2}$)	0.53 ± 0.07	0.56 ± 0.07	0.61 ± 0.08*	0.0008
LedI ($cm \cdot m^{-2}$)	4.83 ± 0.47	4.73 ± 0.71	4.74 ± 0.39	0.7
Sphericity index (%)	57 ± 7	58 ± 8	59 ± 7	0.6
RWT (%)	39 ± 6	42 ± 7	44 ± 7*	0.05
MI, M-mode ($g \cdot m^{-2}$)‡	90 ± 20	97 ± 25	121 ± 24*†	0.0001

*p < 0.05 versus normotensive group. †p < 0.05 versus white coat hypertensive group. ‡M-mode echocardiograms were analyzed in 29 subjects in the normotensive group, 23 in the white coat hypertensive group, 21 in the ambulatory hypertensive group. Data presented are mean value ± SD. DedI = end-diastolic short-axis inner diameter index; hedI = end-diastolic mean wall thickness index; LedI = end-diastolic long-axis index; MI, M-mode and MI, 2DE = mass index determined by M-mode and two-dimensional echocardiography, respectively.

cantly among study groups (Table 3). The velocity of circumferential fiber shortening was significantly higher in the ambulatory hypertensive than in the normotensive group, but it did not differ significantly between the white coat and normotensive groups. However, end-systolic wall stress was significantly higher in the white coat than in the normotensive group.

Left ventricular mass was significantly higher in the ambulatory hypertensive group than in the other two groups (Table 4). Sphericity index did not differ among groups.

The mitral flow pattern was not significantly different among groups (Table 5) except for a shortened deceleration time of early flow in the white coat group and a high peak velocity of late flow in the ambulatory hypertensive group. The peak velocity of diastolic pulmonary venous flow was higher in the white coat than in the ambulatory hypertensive group (Table 6), and the velocity-time integral of diastolic pulmonary venous flow was significantly lower in the ambulatory hypertensive than in the normotensive group. The peak velocity and the velocity-time integral of the flow reversion during atrial systole were significantly higher in the white coat than in the normotensive group. Variables of flow reversion during atrial systole in the ambulatory hypertensive group were intermediate between those in the other two groups.

Table 5. Left Ventricular Filling Variables: Mitral Flow

	Normotensive Group (n = 31)	Hypertensive Groups		p Value
		White Coat (n = 24)	Ambulatory (n = 20)	
E ($cm \cdot s^{-1}$)	64 ± 13	68 ± 14	71 ± 12	0.18
E-dec (ms)	201 ± 38	169 ± 28*	195 ± 49	0.01
A ($cm \cdot s^{-1}$)	55 ± 11	62 ± 16	65 ± 10*	0.03
E/A	1.19 ± 0.27	1.16 ± 0.32	1.12 ± 0.25	0.7
A-d (ms)	122 ± 29	117 ± 20	114 ± 23	0.5

*p < 0.05 versus normotensive group. †p < 0.05 versus white coat hypertensive group. Data presented are mean value ± SD. A = late mitral flow peak velocity; A-d = late mitral flow duration; E = early mitral flow peak velocity; E-dec = early mitral flow deceleration time.

Table 6. Left Ventricular Filling Variables: Pulmonary Venous Flow

	Normotensive Group (n = 30)	Hypertensive Groups		p Value
		White Coat (n = 23)	Ambulatory (n = 19)	
S ($cm \cdot s^{-1}$)	51 ± 11	59 ± 14	52 ± 9	0.05
S-vti (cm)	14 ± 4	16 ± 5	16 ± 4	0.2
D ($cm \cdot s^{-1}$)	47 ± 12	49 ± 10	40 ± 10†	0.01
S/D	1.17 ± 0.41	1.22 ± 0.29	1.34 ± 0.34	0.3
D-vti (cm)	11.2 ± 3.2	9.7 ± 2.8	8.3 ± 2.5*	0.004
PVa ($cm \cdot s^{-1}$)	21 ± 5	28 ± 6*	25 ± 6	0.0001
PVa-vti (cm)	1.79 ± 0.58	2.58 ± 0.94*	2.04 ± 0.92	0.003
PVa-d (ms)	101 ± 26	117 ± 32	100 ± 30	0.08

*p < 0.05 versus normotensive group. †p < 0.05 versus white coat hypertensive group. Data presented are mean value ± SD. D = peak velocity of diastolic pulmonary venous flow; D-vti = velocity-time integral of diastolic pulmonary venous flow; PVa = peak velocity of the flow reversion during atrial systole; PVa-d = duration of the flow reversion during atrial systole; PVa-vti = velocity-time integral of the flow reversion during atrial systole; S = peak velocity of systolic pulmonary venous flow; S-vti = velocity-time integral of systolic pulmonary venous flow.

Left ventricular filling variables were not significantly associated with left ventricular mass, velocity of fiber shortening and ambulatory daytime systolic pressure. The peak velocity of flow reversion during atrial systole correlated with heart rate ($r = 0.34$, $p < 0.01$) and the peak velocity of diastolic pulmonary venous flow correlated with ambulatory daytime diastolic pressure ($r = 0.53$, $p < 0.01$). Several variables of left ventricular filling were significantly related to arterial pressures recorded during the echocardiographic examination (oscillometric arterial pressures); however, although these correlations were pronounced in the white coat group and to some degree significant in the normotensive group, they were not significant in the ambulatory hypertensive group (Table 7).

Reproducibility. The coefficient of variability and the 95% limits of agreement for the following variables comprise variability due to recording analysis as well as biologic variability:

Table 7. Matrix of Correlation Coefficients (r) Between Oscillometric Arterial Pressures and Variables of Left Ventricular Filling in Subjects With White Coat Hypertension

	Osc SP (r)	Osc DP (r)
E ($cm \cdot s^{-1}$)	0.06	−0.31
E-dec (ms)	0.31	0.04
A ($cm \cdot s^{-1}$)	0.67†	0.43*
E/A	−0.72†	−0.79†
A-d (ms)	0.21	0.18
S ($cm \cdot s^{-1}$)	0.40*	0.45*
S-vti (cm)	0.33	0.39
D ($cm \cdot s^{-1}$)	−0.29	−0.49*
S/D	0.51†	0.68†
D-vti (cm)	−0.53†	−0.71†
PVa ($cm \cdot s^{-1}$)	0.40	0.45*
PVa-vti (cm)	0.13	0.31
PVa-d (ms)	−0.37	−0.33

*p < 0.05. †p < 0.01. Osc DP and Osc SP = oscillometric diastolic and systolic arterial pressure, respectively; other abbreviations as in Tables 5 and 6.

oscillometric systolic pressure (6; 5 ± 14 [coefficient of variation; 95 limits of agreement]), oscillometric diastolic pressure (7; 3 ± 9), Doppler velocity-time integral of aortic root flow (10; 0.6 ± 5), aortic annulus diameter (2.5; 0.02 ± 0.1), left ventricular total power (17%; 170 ± 480), steady power (17%, 128 ± 393), oscillatory power (24%; 42 ± 116), left ventricular end-diastolic long-axis (7%; −0.4 ± 1.3), short-axis diameter (5%; 0.12 ± 0.5), wall thickness (14%; 0.07 ± 0.27). Left ventricular end-diastolic volume (21%; 0.65 ± 64), end-systolic volume (21%; −2.5 ± 24), stroke volume (16%; 4 ± 29), ejection fraction (8%; 3 ± 10) and left ventricular mass (18%; 15 ± 63) all determined according to the cylinder-hemiellipsoid formula (Formulas 4 and 5).

Discussion

A definition of white coat hypertension that assumes a completely normal cardiovascular status during everyday life may implicate a lower ambulatory blood pressure cutoff point than that used in this study (10). However, because there is no general agreement on the definition of white coat hypertension, we used procedures current in this hospital to select subjects with white coat hypertension, even though this definition may include subjects with mild hypertension.

Our subjects with hypertension in the general practitioner's office but "normal" ambulatory daytime pressures had an arterial pressure increase during the measurement of arterial pressures by a nurse and during the echocardiographic examination. The pressure response during echocardiography was associated with increased left ventricular external work and left ventricular wall stress and alterations of left ventricular filling; however, left ventricular stroke volume, ejection fraction and velocity of circumferential fiber shortening were not different from values in a normotensive and an ambulatory hypertensive control group.

Left ventricular systolic function, whose final goal is the delivery of cardiac output, is determined by myocardial contractility, afterload, preload and heart rate (32). Variables like ejection fraction and velocity of circumferential fiber shortening, commonly used to evaluate left ventricular systolic function, are influenced by several of these determinants. When the aim is to evaluate myocardial contractility specifically, it has been recommended that these variables be related to end-systolic wall stress (33). Analyzed in this way, subjects with borderline and mild hypertension may have supernormal myocardial contractility (34,35). However, a thorough theoretic analysis of left ventricular mechanics showed that these results may be erroneous because left ventricular wall thickness differs between hypertensive and normotensive subjects (36–38). It has therefore been recommended that midwall instead of endocardial mechanics be used in such analyses. With this approach it was shown that subjects with apparently increased myocardial contractility had normal or depressed contractility, a finding more in accordance with results from studies on isolated myofibers from hypertrophic ventricles (39). This observation may have consequences for the interpretation of systolic function in the subjects with ambulatory hypertension in the present study, who had increased left ventricular wall thickness. However, because left ventricular mass and wall thickness in the white coat hypertensive group were not significantly different from values in the normotensive group, increased left ventricular mechanics in this group may be interpreted as an expression of increased myocardial contractility. The most plausible explanation for this increased myocardial contractility is neuroendocrine stimulation to support the delivery of an adequate stroke volume against an increased external work load. It may also be important that the subjects with white coat hypertension had evidence of increased left ventricular end-diastolic pressure, as discussed later. However, their normal left ventricular end-diastolic volume indicates that the Frank-Starling principle was not an important regulating mechanism in this situation (40,41).

Previous studies (42) have obtained different results regarding factors related to alterations of left ventricular filling. The present study does not support the view that heart rate, ambulatory arterial pressures, left ventricular mass and velocity of circumferential fiber shortening are important in this regard. Arterial pressures recorded during echocardiography were correlated with the ratio of systolic to diastolic pulmonary venous flow peak velocities and inversely related to the ratio of early to late mitral flow peak velocities; however, these correlations were pronounced in the white coat hypertensive group, but were not significant in the ambulatory hypertensive group. These findings are in accordance with previous studies in which similar changes of filling patterns were observed after an acute increase in left ventricular afterload (43,44) and may be due to a slowing of myocardial relaxation (45,46).

The increased pulmonary venous flow reversal in the white coat group could be an indication of decreased ventricular compliance (43,44,47). However, because late mitral flow velocities also increased in these subjects, the findings might indicate increased atrial emptying during atrial systole. Increased left atrial pressure generation during atrial contraction due to neuroendocrine activation may have contributed to this change, but increased atrial preload due to redistribution of blood volume from early to late diastole may have played an additional role.

Methodologic considerations. All variables representing pressure-flow relations in this study were calculated by use of arterial pressures measured during the echocardiographic examination with the oscillometric technique. These pressures tended to be lower than the respective clinic arterial pressures because the former were measured with the subject in the left lateral decubitus position and the latter with the subject in the sitting position. Because all subjects were examined in the same position, we did not correct for the hydrostatic effect between cuff and aortic root.

Clinical implications and conclusions. This study emphasizes the potential confounding effect of the white coat arterial pressure response in studies on heart disease. It may also indicate the potential adverse effects of an acute elevation of arterial pressure in subjects with coronary heart disease. We believe that the arterial pressure response in subjects with white coat hypertension is associated with increased left ventricular external work, increased end-systolic wall stress, in-

creased myocardial contractility and alterations of left ventricular filling.

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